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Impact of Mixed Solvent on Co-Crystal Solubility, Ternary Phase Diagram, and Crystallization Scale Up

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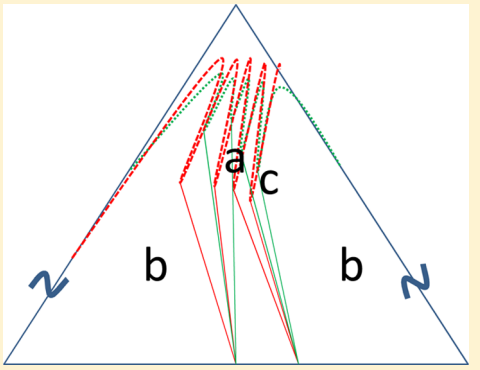
Supporting Information

ABSTRACT: This contribution covers the identification, understanding, and rationale of the interplay between the choice of mixed solvent on the crystallization of the co-crystal system benzoic acid and isonicotinamide (BZ:INA). A critical first step was gauging the impact of solvent choice and composition on the overall crystallization process, across a number of temperature points. This required defining the solubility and phase diagrams of the co-crystal system at specified temperatures, which reflects the cooling crystallization profile encountered in a batch crystallization step. To this end, identifying and understanding the impact of solvent composition over a selected temperature range on the solubility of co-crystal underpins this contribution.



INTRODUCTION

Significant literature exists on the design and synthesis of co-crystals and the application of co-crystals in drug development.[1] However, the focus of this contribution centers on the area of bulk crystallization and the scale up of the solution crystallization route. This aspect of co-crystal research is presently an unexplored area, but critical insight is required if co-crystals are to be routinely isolated from solution and used in the fine chemical and pharmaceutical sectors.

The motivation for considering the application of co-crystals as a dosage form stems from the need to generate stable crystalline material in order to have selectivity and control over the chemical and physical properties of drug entities,[1] specifically, increasing the solubility and manipulating the dissolution profile in order to improve bioavailability. Allied to this is the notion that the solubility of the drug is related to drug absorption, and in the crystallization process there is a need to have knowledge of the solubility profiles and many studies had been carried out and reported.[2] These have focused on the trends of polymorph solubility, dissolution and thermodynamic behavior, and the impact of thermodynamic and kinetic factors on the formation of different polymorphs.[3] This study is the natural progression of these types of concepts for polymorphic systems to co-crystal systems.

The purpose of this work is to examine the role of solvent and a mixed solvent composition on the solution co-crystallisation process. We have chosen the isonicotinamide (INA) and benzoic acid (BA) co-crystal system, as much literature exists in the determination of co-crystal growth from these two compounds in a single solvent and the impact of component ratio through complex formation of the 1:1 and 2:1 complexes.[4,5] It has been previously reported how differences in solubility of the compounds map onto the profile of a typical ternary phase diagram for a 1:1 co-crystal, with compounds with different solubility mapping to the formation of a skewed phase diagram.[6] We report here a more complex situation where a co-crystal has both a 1:1 and 2:1 complex, when a mixed system is employed, and will examine the impact of this in designing the co-crystallisation isolation step.

We report specifically on the impact of a (i) mixed solvent through manipulating the solubility of coformers and molecular complexes and (ii) the impact of composition on the compounds as defined by the ternary phase diagram and how these contribute to the design of the crystallization for this class of compounds.

The solubility of co-crystals in a 1:1 and 2:1 composition in the mixed solvents was analyzed and determined by a single mathematical equation, and data were fitted to the cosolvency model of the general single model (GSM).[7] In order to determine the thermodynamic factors that control the formation of these molecular systems, the change in enthalpy

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and entropy in solution was determined using the van't Hoff equation.

MATERIALS AND METHODS

For further details on the experimental details, see Supporting Information and the Redhas thesis.[8]

All chemicals were purchased from Sigma-Aldrich in the highest purity and were used as supplied.

Co-crystals were grown in water, ethanol, and an ethanol/water solvent (30−90% ethanol). The products were characterized by powder X-ray diffraction (PXRD), Raman, infrared, and ^{1}H NMR spectroscopy.

Solubility. The Jouyban−Acree model was used to predict the solubility of co-crystal,[8−11] and the solubility was also determined experimentally (see Supporting Information).

X-ray Powder Diffraction. Samples were analyzed using a Bruker D8 diffractometer (wavelength of X-ray 0.154 nm Cu source). The solids were scanned from 5−50°, with a 0.01 step width and 1 s time count. The receiving slit was 1°, and the scatter slit was 0.2°.

Solubility Determination. The React-Array Microvate (low throughput) was used to determine the solubility. The samples were placed in glass tubes, and the solutions were stirred at temperatures of 25, 35, and 40 °C, the samples were held at these temperatures for 80 h, and then the solubility was determined gravimetrically.

The predicted solubility in the mixed solvent was calculated using the Jouyban−Acree model, and the deviation from the experimental solubility was determined.[12,13]

Phase Diagram. The screen method developed by Blagden and Boyed et al. was used for this study.[5,14] The RUMED incubator was used to incubate the slurry solution for 2 weeks, and the phases were determined with PXRD.

The ternary phase diagram was constructed at 20 and 40 °C, in 50% ethanol, and the solids were analyzed using PXRD. These ternary phase diagram was plotted using the ProSim software ternary diagram plot.[16]

The phase diagrams, along with the solubility at 50% ethanol solution composition, were subsequently employed to design the cooling crystallization at 100 cm^3 volume.

RESULTS AND DISCUSSION

Solubility. First, the solubility of benzoic acid, isonicotinamide, and 1:1 and 2:1 co-crystals at 25 and 40 °C was determined in water, ethanol, and a water/ethanol mixed solvent (30−90% ethanol), and the change in the solubility was observed. Second, for completeness the direct solubility of the co-crystals and coformers in a mixed solvent was also analyzed, and a hyperbolic solubility profile was observed; the values in pure solvent agree with those previously reported.[5]

In order to undertake the van't Hoff equation, an analysis of the solubility curves of the co-crystal was redrawn such that ln solubility vs 1/temp was plotted, and the profiles for solubility are given in Figure 1a and Figure 1b for the 1:1 and 2:1 co-crystals, respectively (see Supporting Information).

Solubility Behavior of Co-Crystal Coformers in a Mixed Solvent System. The solubility behavior of the 1:1 and 2:1 co-crystals was examined as the water to ethanol content was varied. For both co-crystals, the solubility was at a minimum in water and increased as the solvent composition approached 70% v/v and decreased as the ethanol composition increased. The trend was highly distinctive for the 2:1 co-crystal system (Figure 2).

The trends in molar enthalpy and entropy for both the 1:1 and 2:1 co-crystal systems (Figure 2) are similar for both systems, and the enthalpy is consistent and does not change as the ethanol concentration is increased; however, a notable variation is seen as the concentration of ethanol is increased.

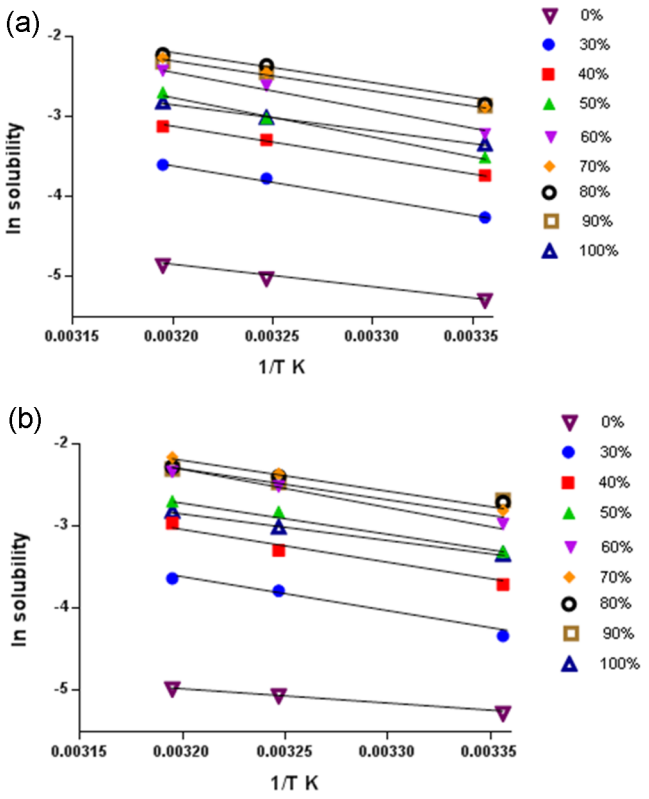

Figure 1. (a) Change in the solubility of co-crystal (1:1) with the inverse of the change of temperature. (b) Change in the solubility of co-crystal (2:1) with the inverse of the change of temperature.

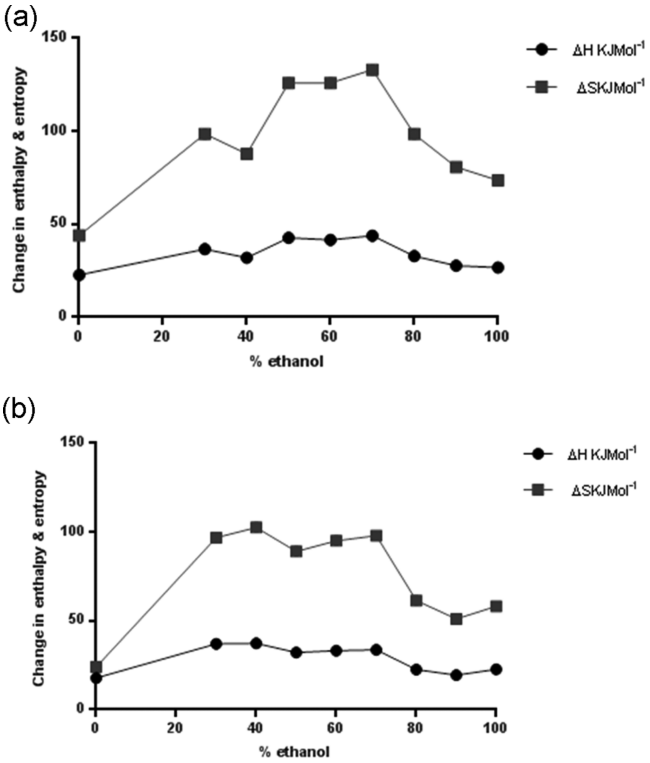

Figure 2. (a) Change in ΔH molar enthalpy of solution, ΔS molar entropy of solution of co-crystals 1:1 in solution. (b) Change in ΔH the molar enthalpy of solution, ΔS the molar entropy of solution of co-crystals 2:1 in solution.

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The implication of these profiles is that the mode of assembly (e.g., hydrogen bond usage and solute solvent interaction) is consistent between the levels of association, i.e., monomers, dimers, chains, etc.; however, the level of assembly varies with regard to the solvation cage and molecular association. This inference is consistent, with a similar mode assembly between the 1:1 and 1:2 occurring in the solution, mirroring the mode of assembly in the crystal structures, in that the enthalpy has a similar but less marked behavior to entropy.

Another approach to the solubility trends is to model solubility in a mixed solvent. A current model used to determine solubility in mixed solvents is the Jouyban–Acree model.[7] A generic model based on the Jouyban–Acree model was developed by training using the literature data for an ethanol/water mixed solvent (see Supporting Information). The model gives poor results for this system because of the two coformers, which overcomplicates the system.

Summary of Solubility Trends. The deviation of the actual solubility from the ideal solubility may indicate that there is a solute–solvent interaction. This suggests that it is critical to obtain verification of nonideal contribution, which may be achieved by examining the deviation from idealities of the measured solubility's (W) to those of the calculated ideal (Q) at a specific temperature (deviation taken as W/QT = solubility in mixed solvent/log–linear model at specific temperatures, see Supporting Information).

For this reason the deviation in actual solubility from the ideal solubility obtained by the ratio of experimental solubility with the ideal solubility calculated using solvent fraction and solute coformer solubility in the respective pure solvents was examined at 25 °C (blue), 35 °C (red), and 40 °C (green) Figure 3a (1:1) and Figure 3b (2:1).

This approach clearly verifies the observations seen with the solubility fitting, whereby two distinct variable solutions regimes exist, and these are dependent on temperature, irrespective of the stoichiometric ratio. This type of trend also suggests that the water breaks up the association and thus affects the balance of monomers versus dimers, etc., as does increasing the temperature, and this is supported by the profiles obtained as the amount of water is increased (Figure 3).

Optimising the Solution Crystallization Conditions. The phase diagrams and subsequent crystallization studies focused on the 40 to 20 °C temperature range, and these were undertaken in an ethanol–water composition determined by the solubility studies; all solutions prior to crystallization were saturated at 40 °C and taken to 50 °C to ensure complete dissolution. The clearest way to extract the initial solvent composition point was to examine the solubility profiles and to confirm the % composition point, for this work 50% was identified. This was undertaken in order to maximize the hypothetical yield, which for our purposes was the highest possible amount of material in solution, and typically this was around 45–55%. From this starting point, two linked studies were undertaken, (i) slow cooling from 50 °C at a rate of 1 to 0.5 °C, to determine the point at which crystallization occurs; this is taken as the under cooling point for our purposes, Figures 4a and 5a, and (ii) step cooling crystallizations from 50 °C to the identified under cooling point, to determine the time for crystallization to occur; which relates to the induction time, Figures 4b and 5b. This is taken as the induction time for crystallization for our purposes.

For the 1:1 system, the curve profile shows that the temperature was at its lowest when the co-crystals were grown

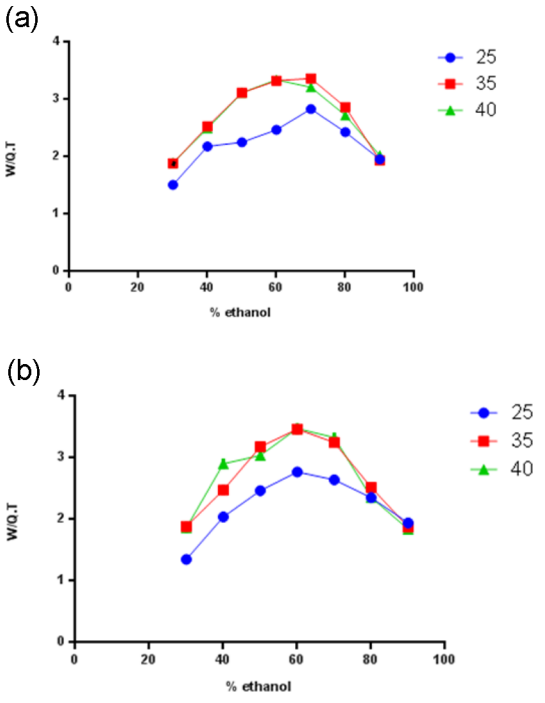

Figure 3. (a) Deviation of the solubility of co-crystals (1:1) in the mixed solvent from ideal solubility. (b) Deviation of the solubility of co-crystals (2:1) in the mixed solvent from ideal solubility.

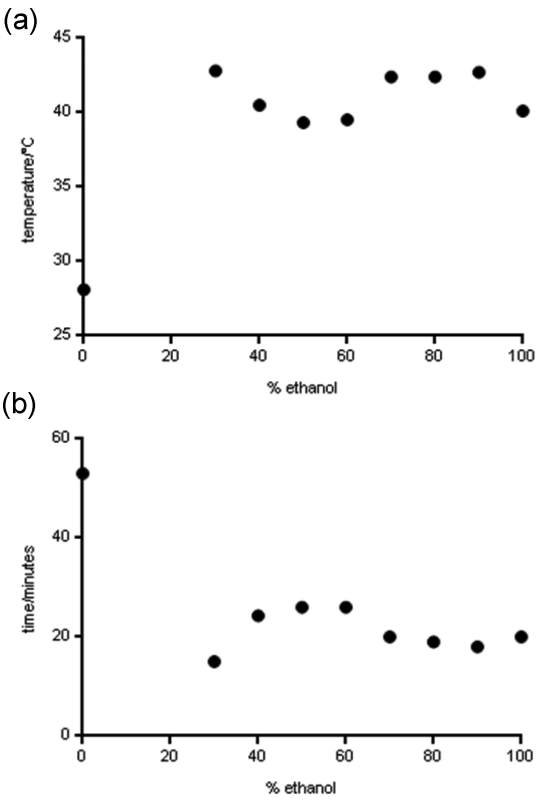

Figure 4. (a) Onset crystallization temperature, relates to the undercooling from 50 °C, BZ:INA (1:1) in water, ethanol, and ethanol/water mixture. (b) Induction time required to start crystallization from the undercooling point from BZ:INA (1:1) in water, ethanol, and ethanol/water mixture.

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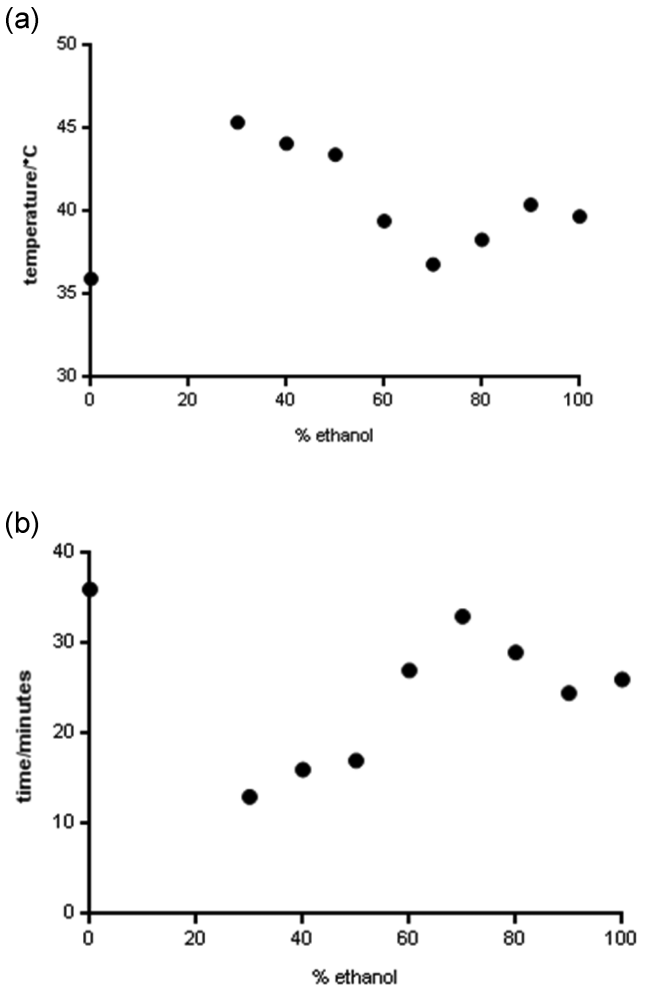

Figure 5. (a) Onset crystallization temperature relates to the undercooling from 50 °C of BZ:INA (2:1) in water, ethanol, and ethanol–water mixture. (b) Induction time required to start crystallization from the undercooling point from of BZ:INA (2:1) in water, ethanol, and ethanol–water mixture.

in water at 28 °C, as the concentration of ethanol was increased the temperature increased sharply in the 30% ethanol solvent and reached 42.8 °C, while the temperature fluctuated between 39.3–42.8 °C at higher ethanol concentration. The maximum time for the start of crystallization in water was 53 min (Figure 4), and the time in 30% ethanol–water mixture was 15 min. The time for the onset of crystallization was found to have increased to 26 min at 50–60% ethanol, and it fluctuated as the concentration of ethanol was increased.

For the 2:1 system the curve profile shows that the crystallization onset temperature in water was low (36 °C), and the temperature increased to 45.4 °C in 30% ethanol, and the temperature dropped to 36 °C in the 70% ethanol solvent and fluctuated as the concentration of ethanol was increased. The curve profile for the induction time for the 2:1 co-crystal indicates that the maximum time required for the start of crystallization in water was 39 min, the time dropped sharply to 15 min in the 30% ethanol mixture, and the time of crystallization increased to 30 min at 50–60% ethanol concentration and decreased further as the concentration of ethanol was increased to around 22 min.

These overall sets of undercooling and induction time data indicate that in pure water the crystallization process would proceed more rapidly than at other solution compositions, and with less under cooling. In addition, the 1:1 system at greater than 50% ethanol appears to behave consistently, whereas the 2:1 system over a similar composition range appears to go through a maximum and then decrease over the same composition range. This may be a facet of a kinetic of the crystallization process of this system, and therefore the phase diagram for this system was re-evaluated at 20 °C and also at 40 °C. These two phase diagrams were then taken as the thermodynamic start and end point of the step cooling crystallization process.

The Ternary Phase Diagram at 20 and 40 °C. The phase diagram at 20 and 40 °C shows a skewed profile at both temperatures, which reflects the differences in the solubility in 50% ethanol of benzoic acid and isonicotinamide. Similar work carried out by Seaton et al.[5] in pure solvents at 25 °C showed that the phase diagram in the water system was heavily skewed, but both 1:1 and 1:2 phases can be grown, while in the ethanol system only co-crystals 1:1 were grown and was less skewed.

The solubility within the phase diagrams at the two temperatures defines the start and end point for a temperature drop cooling crystallization. To link the two isothermal points of the phase diagrams with thermodynamic phase equilibrium points during the step crystallization process, it is important to recognize the deviation in the solubility line between the two temperatures, in defining the labile region during the step cooling process which drives supersaturation. This schematic was derived from overlaying the two phase diagram with the scaling focused upon the eutectic/solubility regions over the region which defines 1:1 only, 1:1 concurrent with 2:1 and 2:1 only. Figure 6 highlights the viable labile region for the

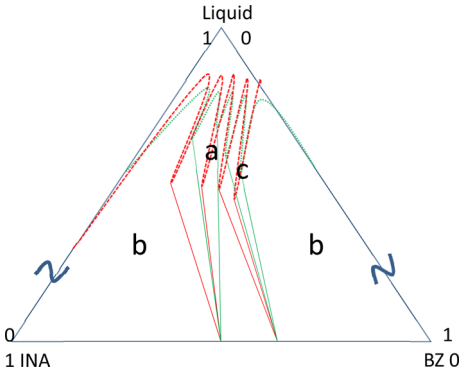

Figure 6. This schematic highlights the deviation between the ternary phase diagrams at 20 °C (dash lines) and 40 °C (solid line). (a) For 1:1, (b) concurrent region, and (c) for 2:1.

crystallization from 40 °C (solid) to 20 °C (dash) for specific solid phase compositions, marked (a) for 1:1, (b) concurrent region, and (c) for 2:1 respectively.

This approach was taken to specify the crystallization conditions in which the system was driven through the labile region at 50 °C, through the phase equilibrium at 40 °C and onto phase equilibrium at 20 °C; these two latter temperature points define the thermal separation employed for these studies. Selection was based upon creating a cooling profile with composition which would establish conditions for crystallization in which one co-crystal phase relation to another could be examined.[16] With regard to the phase diagrams, cooling a solution below its *liquidus* line at tie line requires refined screening to define the transition from one crystal

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composition to another in order to define the tie line boundary[17] and defines the regions on concurrent phase formation. Thus, it is important to use the full set of constructed ternary phase diagrams at various solution compositions to identify the optimum cooling crystallization.

Solution Crystallization – 1:1 to 2:1 Interconversions and Role of Seeding. The details of deviation in the solubility, tie lines, size, and position of the different regions and the eutectic points are presented in Figures 7 and 8. The

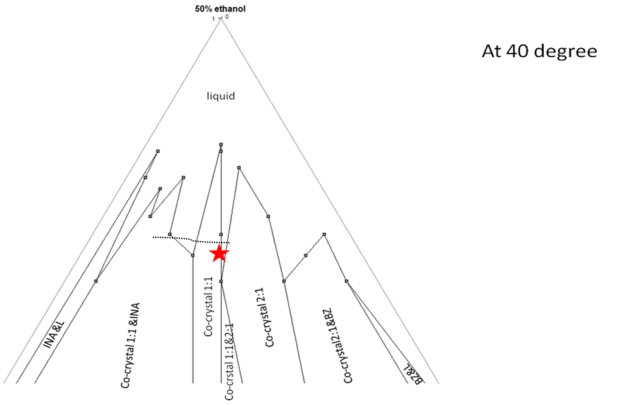

Figure 7. Upper part of the ternary phase diagram of benzoic acid, isonicotinamide, and 50% ethanol at 40 °C (the red point shows the composition of the mixture used in this experiment).

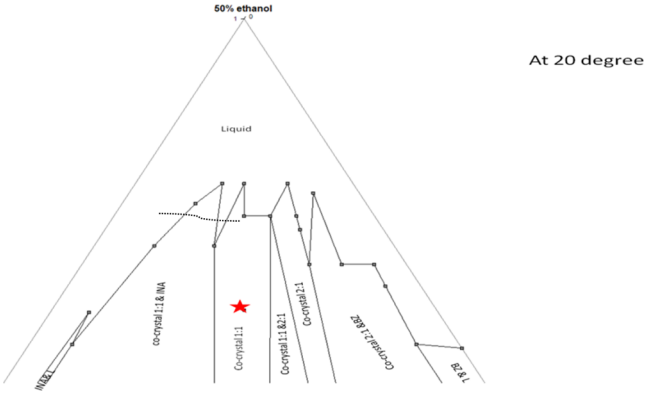

Figure 8. Upper part of the ternary phase diagram of benzoic acid, isonicotinamide, and 50% ethanol at 20 °C (the red point shows the same composition of the mixture used at 20 °C in this experiment).

red star on the liquid solid line identifies where starting at 40 °C would relate to 20 °C for 1:1 co-crystal, e.g., as defined by the detail of the component solubility and eutectics. Gradual cooling shows the formation of co-crystals 2:1 from BZ:INA (1:1) in 50% ethanol, and cooling indicates that the 2:1 product is kinetically favored over the 1:1 co-crystal.

This was confirmed by examining the powder X-ray diffraction pattern of the solid formed during crystallization with and without seeding. These studies indicate that co-crystals 2:1 were grown when the crystals were left to grow for 1 h, the formation of co-crystals 2:1 were kinetically favored, and there was no effect of 1:1 seeds to enhance the growth of co-crystal 1:1 instead of 2:1, but when the crystals were left to grow over a longer period, only formation of the 1:1 co-crystals occurred. This indicates the 1:1 co-crystals were thermodynamically favored. It is for this reason that the isothermal ternary phase diagrams have been redrawn to indicate *meta* stability (Figures 7 and 8), as indicated by the dash line in the upper most portions of the phase regions for 1:1 only, concurrent 1:1 with 2:1 and 2:1 only. The drawn out cooling crystallization in 50% ethanol shows the formation of co-crystals 2:1 from BZ:INA (1:1) in 50% ethanol, and this indicates that this product is kinetically favored over the 1:1 system.

Starting with the physical mixture of BZ:INA (1:1) the monitoring of crystallization confirms the previous report that only 2:1 co-crystals were grown in water and only 1:1 co-crystals were grown in ethanol.[5] When the physical mixture of BZ:INA was set at a 2:1 stoichiometric ratio, and the solvent composition was varied, the crystal screening clearly showed that an increase in the formation of 2:1 co-crystals was noted as the fraction of water increased, and an increase in 1:1 co-crystals was noted as the fraction of ethanol was increased. This leads to the possibility of tuning the crystallization outcome through the selection of an appropriate solvent composition.

To highlight this tuneability opportunity for the crystallization on solvent composition, the phase outcome was monitored, and the solution composition was varied from pure water to pure ethanol for a batch cooling crystallization run. Typical outcomes are presented in Figures 9 and 10. As the

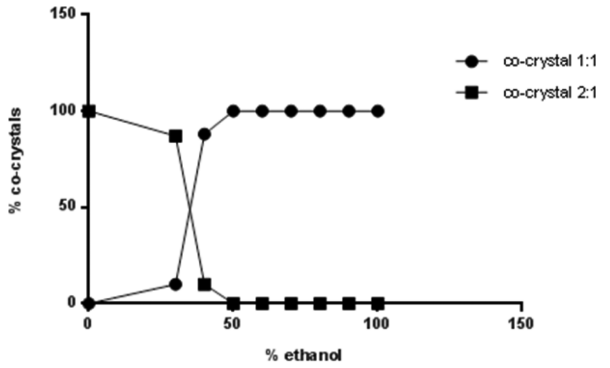

Figure 9. Change in the growth of co-crystals (1:1) and (2:2) from BZ:INA (1:1) with the change of the solvent.

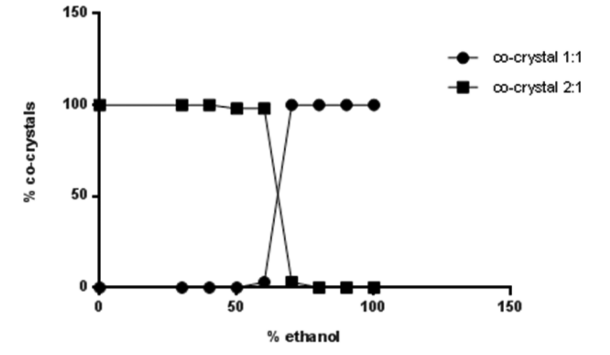

Figure 10. Change in the growth of co-crystals (1:1) and (2:1) from BZ:INA (2:1) with the change of the solvent.

solvent mixture being varied with either a 1:1 or 2:1 compound ratio being set, the dominate phase around 30% and 40% respectively for the ethanol mixed solvent was the 2:1 system, and for 60 to 100% the dominant phase was 1:1 only.

Initially the amount of BZ:INA 1:1 clearly varied as the solvent composition was varied (Figure 9). The curve profile shows that only co-crystals 2:1 were grown in water and only co-crystals 1:1 were grown in ethanol. The growth of 1:1 co-

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crystals started in 30% ethanol and increased as the growth of 2:1 co-crystals decreased with an increase in the concentration of ethanol; however at 60% only 1:1 co-crystals formed.

The curve profile (Figure 10) shows that in water only 2:1 co-crystals were grown and only 1:1 in ethanol. At 50% ethanol there was significant growth of the 1:1 co-crystals, and with an increase in concentration of ethanol this increased and the amount of 2:1 co-crystals decreased. In 100% ethanol only 1:1 cocrytals were grown and at 60% both 1:1 and 2:1 were most significant.

With the seeding studies undertaken, to disrupt inter conversion, the following comparative trends without and with seeding were noted. With the crystallization configured for 1:1 formation, this phase was observed after 1 h. However, repeating with seeds of 1:1 co-crystals the initial appearance of 2:1 as a transient phase was reduced, and conversion to complete 1:1 co-crystals was within 5−10 min. With the crystallization configured for 2:1 formation, this phase was observed after 1 h, and there was no effect of 1:1 seeds to enhance the growth of the 1:1 co-crystal, over the 2:1 within this period.

CONCLUSION

The solubility of both 1:1 and 2:1 co-crystals increased, with an increase in concentration of ethanol and with an increase in temperature. The solubility of the 2:1 co-crystal is greater than the 1:1 co-crystal in the ethanol−water mixtures, in water the solubility is identical, and at higher ethanol concentration the solubility is similar. Overall, the solubility of 1:1 and 2:1 co-crystals was lower than the solubility of the individual components.

Further, this study indicates that the solubility of the 1:1 and 2:1 co-crystals in the mixed solvents was fitted to the general AJ model cosolvency, and the overall fit was within an MPD of 20%; the model does not really work for this class of compounds. Subsequently, fitting to these studies specific data a MPD of less than 10% was achieved. In fact, two classes of solubility appear to be present, and which grouping they belong to was found to be dependent on temperature and solvent composition. This was further highlighted by examining the deviation of the actual solubility from the ideal solubility. Such deviation suggests that there is reconfiguration in solute−solvent interaction during formation of molecular aggregates or the formation of specific modes of molecular complexation, as seen in the solid state. The van't Hoff equation was used to calculate the enthalpy and entropy of solution; the results show that the enthalpy of solution change for the 1:1 co-crystals is higher than that of the 2:1 co-crystals, indicating that the 1:1 co-crystal has more interaction between the solute and the solvent. The entropy of solution change in 1:1 co-crystal is higher than that for 2:1 co-crystal, indicating that the system for the 1:1 co-crystal is more disordered than the 2:1 co-crystals. Therefore, 1:1 co-crystals in the solution state are less stable than that of the 2:1 co-crystals. This further substantiates the role of solvent sensitization on the outcome of co-crystal formation.

The determination of the solubility curves was an important method to differentiate and identify the polymorphic aspect of this system. From the synthesis perspective of co-crystals for this system, opting for water, ethanol, and mixed solvent impacted the formation of pure 1:1 and 2:1 co-crystals, or a mixture from both depending on the solvent composition. These findings clearly support the view that the choice of mixed solvent composition influences the step cooling crystallization process significantly, and undertaking ternary phase diagram at two temperatures which define initial and final point on step cooling profile reveals the complex crystallization behavior of 1:1 or 2:1 co-crystal systems.

For the key crystallization parameters, solubility, induction time, and under cooling, the impact of solvent composition has been demonstrated to go beyond composition of BZ:INA 1:1 and 2:1 obtained but also impacts on the induction time for the crystallization to occur. For instance when the solvent was water, a notable induction time was seen; however, there was a significant decrease in undercooling at 30% ethanol, with the associated observation that the temperature of crystallization was lower in water than ethanol, but of a similar magnitude irrespective of solvent composition. Critically, such outcomes do suggest these patterns with crystallization parameters do trend with the picture of mixed modes of association and solvation noted from the solubility screen.

To conclude, this contribution reveals the complexity of co-crystal formation, for systems with 1:1 and 2:1 co-crystals, and the way in which solvent composition, along with ternary phase diagrams and solubility studies when combined as presented, supports the rational design of the co-crystals crystallization. Future work will be focused on the solution speciation and the impact such speciation has upon the nucleation process for this type of co-crystal system.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.5b00908.

Van't Hoff equation; the log−linear model of Yalkowsky; the Jouyban−Acree model; phase diagram experimental (PDF)

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Notes

The authors declare no competing financial interest.

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